Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 166, 168, 170 and 177 are pending in the application, with claim 166 being the independent claim. Claim 170 has been amended. Support for the amendment to claim 170 can be found at page 52, line 17 through page 53, line 24. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claims 166, 168, 170 and 177 under the judicially created doctrine of obviousness-type double patenting over claims 1-29 of copending Appl. No. 10/031,345. (Office Action, pages 2-3.)

Applicants note that, according to § 804(I)(B) of the Manual of Patent Examining Procedure (M.P.E.P.), when provisional double patenting issues are raised in copending applications, "[i]f the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a 'provisional' double patenting rejection

which will be converted into a double patenting rejection when the one application issues as a patent."

As noted by the Examiner, Applicants will appropriately address the double patenting rejection at a later date, in the event it is converted to an actual double patenting rejection pursuant to MPEP § 804(I)(B). (*See id.*)

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 170 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention. (Office Action, page 3.) In accordance with the Examiner's suggestions, Applicants have amended claim 170 to recite a CTL/HTL epitope conjugate, where the CTL epitope of the conjugate corresponds to the isolated peptide of claim 166, and the HTL epitope of the conjugate corresponds to a non-HCV T helper peptide. Applicants believe that the amended claim 170 sufficiently points out and distinctly claims the subject matter which Applicants regard as the invention. Thus, the Examiner's rejection of claim 170 under 35 U.S.C. § 112, second paragraph, has been rendered moot. Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claim 170 under 35 U.S.C. § 102(e) as allegedly being anticipated by Chien, *et al.* (U.S. Patent No. 6,150,087) ("Chien"). (Office Action, pages 3-4.) Applicants respectfully disagree. However, in order to expedite prosecution,

Applicants have amended claim 170, as noted above, so that claim 170 recites a CTL/HTL epitope conjugate, where the CTL epitope of the conjugate corresponds to the isolated peptide of claim 166, and the HTL epitope of the conjugate corresponds to a non-HCV T helper peptide. Applicants assert that claim 170, as currently amended, is not anticipated by Chien.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). MPEP § 2131. Chien fails to teach every aspect of the claimed invention.

Currently amended claim 170 recites a CTL/HTL epitope conjugate, where the CTL epitope is an isolated peptide selected from a group which includes Applicants' elected peptide GVAGALVAFK. Chien does not disclose the exact peptide sequence GVAGALVAFK. As noted previously, Chien is merely an attempt to cover the HCV genome in 50 amino acid blocks and only discloses a peptide sequence 50 amino acids in length (AA1850-AA1900) which *comprises* the sequence GVAGALVAFK. (*See* Chien, col. 27, second paragraph.) Furthermore, none of the peptides disclosed in Chien corresponds exactly to Applicants' claimed peptide.

In addition, the Examiner has alleged that within the AA1850-AA1900 peptide disclosed in Chien "[t]he amino acids other than GVAGALVAFK inherently constitute a 'T helper epitope.'" (Office Action, page 4.) The Examiner further alleges that "[t]here are tens of thousands of different types of mammalian MHC Class II alleles which bind largely nonoverlapping sets of T helper peptides, therefore it would be inevitable that the

nonGVAGALVAFK amino acids in [AA1850-AA1900] would have at least one T helper epitope." (*Id.*)

Applicants note that currently amended claim 170 recites that the HTL epitope of the claimed CTL/HTL conjugate, corresponds to a **non**-HCV T helper peptide. Chien, as described above, discloses the HCV genome in 50 amino acid blocks, one of these 50 amino acid blocks corresponding to AA1850-AA1900. The sequence AA1850-AA1900 contains only HCV sequence. The HTL epitope of Applicants' CTL/HTL epitope conjugate corresponds to a **non**-HCV sequence. Because the sequence AA1850-AA1900 does not contain non-HCV sequence, Chien does not disclose every element of currently amended claim 170. Thus, claim 170 is not anticipated by Chien.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

I. The Examiner has not established a *prima facie* case of obviousness.

The Examiner has rejected claims 166, 168, 170 and 177 under 35 U.S.C. § 103(a) as allegedly being obvious over Chien in view of Berzofsky *et al.*, U.S. Patent No. 5,980,899 (Berzofsky), and in view of Guo *et al*, *Nature* 360: 364-366 (1992) (Guo). (Office Action, page 4.) Applicants respectfully disagree and traverse the rejection.

In order to establish a *prima facie* case of obviousness, the following three criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a

reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143. Furthermore, without a motivation to combine, a rejection based on a *prima facie* case of obviousness is improper. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants assert that there is no suggestion or motivation to combine the reference teachings, and thus the first criteria necessary to establish a *prima facie* case of obviousness has not been met.

Applicants note that currently pending claims 166, 168, 170 and 177 are directed to an isolated peptide selected from a group which includes Applicants' elected peptide GVAGALVAFK. Chien, as discussed in Applicants' Reply filed November 29, 2004 and further discussed above, does not teach or suggest every element of Applicants' claimed invention. This is supported by the Examiner's own statement that "Chien et al. do not teach the peptide of claim 166/168." (Office Action, page 5.)

The Examiner has alleged that Chien in view of Berzofsky renders claims 166, 168, 170 and 177 obvious. (Office Action, page 4.) Berzofsky describes the cytotoxic T lymphocyte (CTL) response to the NS5 region of the hepatitis C virus using 28 peptides from NS5 which were selected by an amphipathicity algorithm. Berzofsky, Abstract. The Berzofsky article focuses on the NS5 region, teaching that it is desirable to identify CTL epitopes found within this region of HCV. Specifically, Berzofsky states that "no CTL epitopes have yet been defined in any HCV protein. Nevertheless, it has been discovered that the non-structural protein of HCV which corresponds to [NS5] . . . is a relatively conserved target protein for CTL, and, in fact presents an epitope that induces a cytotoxic T cell response in lymphocytes." Berzofsky, col. 5, lines 12-21. There is no

suggestion in Berzofsky that other regions of the HCV genome necessarily contain good targets for CTL. The preferred peptides of Berzofsky, as listed in Fig. 1A, all correspond to peptides of the NS5 region. Berzofsky, Fig. 1A.

In comparison, Applicants' elected peptide is from a different region of the HCV genome, NS4. *See* Specification, Table XXIII. Applicants' elected peptide, GVAGALVAFK, is not discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not teach, or even suggest Applicants' peptide, nor does Berzofsky teach or suggest the techniques Applicants' utilized to identify candidate CTL epitopes. Given the relatively large number of possible epitopes that could be identified within the HCV genome, the Berzofsky article, without more, would not be viewed by one of skill in the art to teach or suggest Applicants' claimed invention. As such, Chien in view of Berzofsky does not render claims 166, 168, 170 and 177 obvious.

The Examiner has also alleged that Chien, in view of Berzofsky, and further in view of Guo allegedly renders claims 166, 168, 170 and 177 obvious. (Office Action, page 5.) Guo generally describes how CTL recognize viral peptides complexed with MHC and that these peptides generally are 9 to 11 amino acids in length. Guo, page 364. Guo states that "[f]oreign peptides, such as those from viral infections, complexed with major histocompatibility complex (MHC) molecules present a novel antigenic surface to CTL, and are therefore recognized, stimulating CTL to kill the invaded cell." *Id.* Furthermore, Guo discloses peptide sequences from several proteins including ribosomal 60S, human Hsp70, and influence NP. Guo, Table 1. Guo, however, does not contain

any discussion regarding the identification of CTL epitopes within the HCV genome, nor does Guo disclose Applicants' elected peptide. In addition, Guo states that "[s]tudies of peptides eluted from class I MHC molecules show that nonamers (that is, peptides that are nine amino acids long) are preferred." Guo, page 364, column 2. As such, Guo in fact teaches away from Applicants' elected peptide. While Applicants' elected peptide is the sequence GVAGALVAFK, ten amino acids in length, Guo teaches that preferred peptides are nine amino acids in length. As described further below, an immunogenic response to Applicants' elected peptide GVAGALVAFK is significantly greater than to the nonamer peptide VAGALVAFK, which differs by only one amino acid to the claimed peptide. Thus, such a difference, as demonstrated by the Applicants, can be critical to the binding and immunogenicity of a particular peptide. Therefore, a teaching of Guo indicating that preferred peptides are nonamers, cannot be viewed as providing a suggestion or motivation to teach Applicants' claimed invention.

Accordingly, Chien, in view of Berzofsky, and further in view of Guo provide no motivation or suggestion to combine references, nor do they teach or suggest all of the claim limitations. At best, Berzofsky and/or Guo provide an invitation to experiment.

Thus, Applicants assert that the criteria requiring that a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, has not been met. Therefore, a *prima facie* case of obviousness, with respect to claims 166, 168, 170 and 177, has not been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

II. Even assuming that a *prima facie* case of obviousness has been established, Applicants assert that this *prima facie* case of obviousness can be rebutted.

Assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants assert that the *prima facie* case of obviousness can be rebutted. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F. 2d at 692-93. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP § 716.02; *see In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

As discussed previously in the Amendment and Reply filed November 29, 2004, Table XXIII ("Immunogenicity of identified supermotif-bearing peptides") shows that Applicants' elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. Furthermore, this response is significantly greater than the nonamer peptide VAGALVAFK (56.5 as compared to 7.1) which shares the *identical* sequence with the exception of a glycine amino acid at the N-terminus of the sequence. Applicants also point out that in Table XVI, Applicants' elected peptide GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif.

Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK has unexpected properties. In view of the improved binding properties of GVAGALVAFK

as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that this evidence of unobvious or unexpected advantageous properties is present and is sufficient to rebut a *prima facie* case of obviousness. Furthermore, the concern of the Examiner that "none of the functional attributes referred to by applicant are recited in the claimed invention" is misplaced. It is the functional characteristic of the peptide, as determined by the Applicant, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art. A showing of nonobviousness does not require that these features necessarily need to be present as limitations of the claims.

Based on the above, Applicants assert that even assuming a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness can be rebutted using the evidence described above.

Finally, the Examiner alleges that the peptide of claim 166 is found in the larger peptide taught by Chien, which is immunogenic, and therefore that "the functional attributes of the peptide of claim 166 would presumably be present in the peptide of claim 166." (Office Action, page 7.) Applicants respectfully disagree.

Applicants assert that larger peptides, such as the one disclosed in Chien, may contain more than one epitope which is capable of eliciting an immune response. The immunogenicity of one epitope in a larger sequence may be limited by another more immunogenic epitope within that same sequence. This "immunodominance" of one epitope thus may lead to the suppression of a CTL response specific to another preferred epitope within that same sequence. *See* Yewdell & Bennick, *Annu. Rev. Immunol.*

17:51-88 (1999) (of record as document AR24, IDS, filed March 18, 2004). The larger peptide in Chien therefore may have entirely different functional attributes than Applicants' elected peptide, as the 50 amino acid sequence of Chien (AA1850-AA1900) may contain other epitopes which are immunodominant to the epitope GVAGALVAFK.

In addition, Applicants point out that, although epitopes within a larger sequence can be correctly processed, the yield of processed epitope can differ depending on the positioning of the epitope within a chimeric sequence. Del Val *et al.*, *Cell*, l-66:1145-1153 (1991) (of record as document AT4, Information Disclosure Statement (IDS), filed March 18, 2004)., abstract and 1149, col. 2, 3d full paragraph. Furthermore, Eisenlohr *et al., J.Exp.Med.* 175:481-487 (1992) (of record as document AS6, IDS, filed March 18, 2004) show that flanking residues can influence epitope processing. Eisenlohr *et al.*, abstract. Therefore, an epitope embedded within a larger sequence may be processed differently, and thus have different immunogenicity than the same epitope free of flanking or surrounding amino acid residues. Therefore, the functional attributes of the peptide of claim 166 are not necessarily present in the larger peptide, as the larger peptide may process an embedded peptide differently as a result of additional surrounding residues. Consequently the processed peptide may produce a different immunogenic response.

Accordingly, Applicants assert that Chien, in view of Berzofsky and Guo, do not render claims 166, 168, 170 and 177 obvious as they do not teach or suggest all of the limitations of the claims. Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

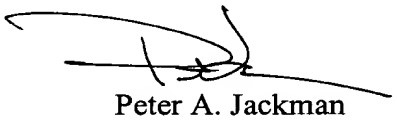
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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